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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,990	HOWE, ALAN	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *15-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Howe, Alan

DETAILED ACTION

Election/Restrictions

The Election filed on November June 29, 2005 in response to the Restriction Requirement of April 19, 2005 has been entered. Applicant's election of Group I, claims 1-14 and 36-38, as specifically drawn to a phosphoprotein reagent and a method of making the phosphoprotein detection reagent has been acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The restriction requirement is therefore deemed to be proper and is made FINAL.

Claims 1-38 are currently pending.

Claims 15-35 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-14 and 36-38 are currently pending.

Species Election

Acknowledgement is made of the election of the following species: Fe^{3+} as the metal ion of claim 5; amino-butyl-nitriloacetic acid (AB-NTA) as the chelator donor molecule from claim 11; and sulfo-N-hydroxysuccinimidyl-biotin (sulfo-NHS-biotin) as the detectable donor moiety from claim 12. Because applicant did not distinctly and specifically point out the supposed errors in the species requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). After careful reconsideration, the species requirement for the metal ion of claim 5 and the chelator donor molecule of claim 11 have been withdrawn.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into

the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

Claims 1 is objected to because of the following informalities: Claim 1 recites "... an detectable label ...." It appears that the letter "a" should replace "an" such that the claim recites "... a detectable label...." Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5 and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by McHahan *et al.* (Analytical Biochemistry 1996; 236: 101-106).

McMahan et al. disclose a conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches (abstract, lines 5-7) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, McMahan *et al.* teach (abstract, lines 8-9) that the detectable moiety is biotin. In addition to the conjugate comprising a chelator-metal ion moiety and a detectable label, McMahan *et al.* teach that the conjugate further comprises a spacer between the chelator-metal ion moiety and the detectable label (page 103, Fig. 1). The reference further teaches that the conjugate is soluble in an aqueous solution (page 104, beginning on 1st column, 1st paragraph to 2nd column). Although McHahan *et al.* does not specifically teach that the conjugate binds to a phosphorylated amino acid residue, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Claims 1-3, 5, 8-9 and 36-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001).

Molecular Probes disclose a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches (page 1, 1st column, Introduction) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, Molecular Probes teach (page 1, 1st column, Introduction) that the detectable moiety is biotin. The reference further teaches (Title) a kit comprising the conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the kit, Molecular Probes teaches that the kit further comprises a secondary reagent for detecting the conjugate (1st page, 1st column, Introduction, lines 11-14), as well as instructions on how to use the kit. Although Molecular Probes does not specifically teach that the conjugate is soluble in an aqueous medium, the claimed functional limitation would be an inherent property of the referenced product because as evidenced by McMahan *et al.* (*supra*), biotin and nitriloacetic acid conjugates are soluble in an aqueous solution (page 104, beginning on 1st column, 1st paragraph to 2nd column). Thus, the claimed "conjugate" appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Furthermore, while Molecular Probes does not specifically teach that the conjugate binds to a phosphorylated amino acid residue, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Claims 1-2, 4-5 and 8-9 rejected under 35 U.S.C. 102(b) as being anticipated by Ehteshami *et al.* (J. Molecular Recognition 1996; 9: 733-737).

Ehtashami *et al.* disclose a conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches that the chelator is iminodiacetic acid (abstract) and the metal is either Cu^{2+} (page 734, 1st column, 3rd paragraph) or Ni^{2+} (page 735, 2nd column, 3rd paragraph). With regards to the detectable moiety, Ehtashami *et al.* teach (abstract) that the detectable moiety is biotin. In addition to the conjugate comprising a chelator-metal ion moiety and a detectable label, Ehteshami *et al.* teach that the conjugate further comprises a PEG spacer between the chelator-metal ion moiety and the detectable label, wherein the presence of the PEG provides water solubility (abstract and page 733, *Introduction*, 1st column, lines 14-15). Although Ehtashami *et al.* does not specifically teach that the conjugate binds to a phosphorylated amino acid residue, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Claims 1-2, 4-5 and 8-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Etheshami (1996 "Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols", Ph.D. dissertation, University of Arizona).

Etheshami et al. disclose (page 83 and 89) a conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety via a PEG spacer group. With regards to the chelator-metal moiety, the reference teaches (page 89) that the chelator is iminodiacetic acid (IDA) and the metal is Cu2+. With regards to the detectable moiety, Etheshami et al. teach (page 83) that the detectable moiety is biotin. The reference also teaches (page 83-84) a method of synthesizing the conjugate comprising contacting iminodiacetic acid (IDA) with a molar excess of NHS-biotin under conditions wherein the biotin is transferred to IDA to form the chelator-detectable moiety complex. Etheshami further teaches (page 89) that the synthesis step further comprises mixing the IDA-PEG-Biotin conjugate in a metal ion containing solution, wherein the conjugate and metal ion are present in an equimolar concentration, i.e. 1:1. Thus, while Etheshami does not specifically teach that the conjugate is soluble in an aqueous solution, the claimed functional limitation would be an inherent property of reference conjugate because as

evidenced by Ehteshami *et al.* (supra), the presence of the PEG spacer between the chelator-metal ion moiety and the detectable label provides water solubility (abstract and page 733, *Introduction*, 1st column, lines 14-15). Thus, the claimed product appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Furthermore, although Ehtashami *et al.* does not specifically teach that the conjugate binds to a phosphorylated amino acid residue, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-9 and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over McHahan et al. (Analytical Biochemistry 1996; 236: 101-106) or Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001) in view of Neville et al. (Protein Science 1997; 6: 2436-2445) and Nieba et al. (Analytical Biochemistry 1997; 252: 217-228).

McMahan et al. disclose, as applied to claims 1-3, 5 and 8-9 above, a conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety, wherein the chelate is nitriloacetic acid, the metal is Ni^{2+}, and the detectable moiety is biotin

(abstract). The reference further teaches that the conjugate is a unique reagent, which can be used for the detection of histidine-tagged proteins (Title).

Molecular Probes teach, as applied to claims 1-3, 5, 8-9 and 36-38 above, a conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety, wherein the chelate is nitriloacetic acid, the metal is Ni^{2+}, and the detectable moiety is biotin (Introduction). The reference further teaches a kit comprising the conjugate as described above.

Neither McMahan et al. nor Molecular Probes teach that the metal ion is either Ga^{3+} or Fe^{3+}.

Nieba et al. teaches that while typically the metals Ni^{2+}, Zn^{2+}, Co^{2+}, and Cu^{2+} are chelated to NTA, the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag (page 217, 2nd column, 1st paragraph).

Neville et al. teaches that Fe^{3+} loaded NTA metal-ion affinity resin preferentially bind to phosphopeptides as compared to His-containing peptides (abstract).

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to substitute a metal ion such as Ga^{3+} or Fe^{3+} as taught by Neville et al. in view of Nieba et al. One would have been motivated to do so because as taught by Nieba et al., the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag. For example, Neville et al. teaches that Fe^{3+} loaded NTA and IDA metal-ion affinity resin preferentially bound to phosphoproteins as compared to His-containing peptides. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting the metal ion as taught by McMahan et al. or Molecular Probes in view of Nieba et al., one would achieve a metal chelate which recognizes other proteins, such as phosphoproteins, which do not contain a His tag.

Claims 1-2 and 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ehteshami et al. (J. Molecular Recognition 1996; 9: 733-737) or Etheshami (1996 "Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols", Ph.D. dissertation, University of Arizona)in view of Neville et al. (Protein Science 1997; 6: 2436-2445) and Nieba et al. (Analytical Biochemistry 1997; 252: 217-228).

Ehtashami et al. disclose, as applied to claims 1-2, 4-5 and 8-9 above, a conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety,

wherein the chelate is iminodiacetic acid, the metal is either Cu^{2+} or Ni^{2+}, and the detectable moiety is biotin (abstract). The reference further teaches that the conjugates are useful for immobilized metal affinity chromatography (IMAC) (abstract).

Etheshami et al. disclose (page 83 and 89) a conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety via a PEG spacer group. With regards to the chelator-metal moiety, the reference teaches (page 89) that the chelator is iminodiacetic acid (IDA) and the metal is Cu2+. With regards to the detectable moiety, Etheshami et al. teach (page 83) that the detectable moiety is biotin. The reference also teaches (page 83-84) a method of synthesizing the conjugate comprising contacting iminodiacetic acid (IDA) with a molar excess of NHS-biotin under conditions wherein the biotin is transferred to IDA to form the chelator-detectable moiety complex. Etheshami further teaches (page 89) that the synthesis step further comprises mixing the IDA-PEG-Biotin conjugate in a metal ion containing solution, wherein the conjugate and metal ion are present in an equimolar concentration, i.e. 1:1. The reference further teaches that the conjugates are useful for immobilized metal affinity chromatography (IMAC) (abstract, page 20)

Neither the Ehtashami et al. or Ehtashami teach the metal ion as being either Ga^{3+} or Fe^{3+}.

Nieba et al. teaches that while typically the metals Ni^{2+}, Zn^{2+}, Co^{2+}, and Cu^{2+} are chelated to IDA, the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag (page 217, 2nd column, 1st paragraph).

Neville et al. teaches that Fe^{3+} loaded IDA metal-ion affinity resin preferentially bind to phosphopeptides as compared to His-containing peptides (abstract).

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to substitute a metal ion such as Ga^{3+} or Fe^{3+} as taught by Neville et al. in view of Nieba et al. One would have been motivated to do so because as taught by Nieba et al., the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag. For example, Neville et al. teaches that Fe^{3+} loaded NTA and IDA metal-ion affinity resin preferentially bound to phosphoproteins as compared to His-containing peptides. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting the metal ion as taught by Ehtashami et al. in view of Nieba et al., one would achieve a metal chelate which recognizes other proteins, such as phosphoproteins, which do not contain a His tag.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
8/19/05